Random death process for the regularization of subdiffusive anomalous equations

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Subdiffusive fractional equations are not structurally stable with respect to spatial perturbations to the anomalous exponent (Phys. Rev. E 85, 031132 (2012)). The question arises of applicability of these fractional equations to model real world phenomena. To rectify this problem we propose the inclusion of the random death process into the random walk scheme from which we arrive at the modified fractional master equation. We analyze the asymptotic behavior of this equation, both analytically and by Monte Carlo simulation, and show that this equation is structurally stable against spatial variations of anomalous exponent. Additionally, in the continuous and long time limit we arrived at an unusual advection-diffusion equation, where advection and diffusion coefficients depend on both the death rate and anomalous exponent. We apply the regularized fractional master equation to the problem of morphogen gradient formation.

Anomalous subdiffusion, where the mean squared displacement grows sub-linearly with time $\langle x^2(t) \rangle \sim t^\nu$, where the anomalous exponent $\nu < 1$, is an observed natural phenomena [1]. It is seen in areas as varied as dispersive charge transport in semi-conductors [2], ion movement in spiny dendrites [3], protein transport on cell membranes [4]. In the classical paper [5], Metzler, Barkai, and Klafter introduced the fractional Fokker-Planck equation (FFPE) that describes anomalous subdiffusion of particles in an external field, $F(x)$. This equation for the probability density $p(x, t)$ is written as $\frac{\partial p}{\partial t} = \mathcal{D}_t^{1-\nu} L_{FP} p(x, t)$, where $L_{FP} = K_\nu \left[\frac{\partial^2}{\partial x^2} - \frac{\partial}{\partial x} \frac{F(x)}{k_B T} \right]$ is the Fokker-Planck operator, K_ν is the anomalous diffusion coefficient and $\mathcal{D}_t^{1-\nu}$ is the Riemann-Liouville fractional derivative of order $1 - \nu$, defined as

$$\mathcal{D}_t^{1-\nu} p(x, t) = \frac{1}{\Gamma(\nu)} \frac{\partial}{\partial \tau} \int_0^t \frac{p(x, \tau) d\tau}{(t - \tau)^{1-\nu}}. \qquad (1)$$

It was shown that the external field $F(x)$ leads to a stationary solution to the FFPE in the form of the Boltzmann distribution [6]. However, in a recent paper [7], we have demonstrated that this fundamental result is not structurally stable with respect to spatial variations of the anomalous exponent ν. Small, non-homogeneous in space, variations of ν destroy the stationary solution to the FFPE. In fact, even the simple one-dimensional fractional subdiffusion equation with constant anomalous exponent and $F(x) = 0$, in the finite domain $[0, L]$ with reflective boundary conditions, is structurally unstable. This equation should give a uniform stationary distribution over the interval $[0, L]$ in the long-time limit. However, if we use slightly non-uniform anomalous exponent $\nu(x)$, the probability density $p(x, t)$ will be completely different from the uniform distribution: as $t \to \infty$ it concentrates at the point where $\nu(x)$ has a global minimum on $[0, L]$. We called this phenomenon anomalous aggregation [8]. Since it is impossible to have a completely homogeneous environment, in which ν is uniform, the question arises as to whether the fractional equations with constant anomalous exponents are useful models for any real phenomena involving subdiffusion. This question is

of great importance for the problem of a morphological patterning of embryonic cells, which is controlled by the distribution of signaling molecules known as morphogens [9–11]. To ensure robust pattern formation, the morphogen gradients must be structurally stable with respect to the spatial variations of environmental parameters including the anomalous exponent. Note that the unusual behavior of subdiffusive transport has been observed in an infinite system with two different values of anomalous exponents [12].

To rectify the structural instability involving unlimited growth of $p(x, t)$, at the point of minimum of anomalous exponent $\nu(x)$, we need a regularization of the fractional equations. The standard approach to regularize the fractional subdiffusive equations is to temper the power law waiting time distribution in a such way that the normal diffusion behavior in the long-time limit is recovered (see, for example, [13]. In this case, by suppressing the power law behavior, the intrinsic characteristics of the anomalous process are lost. In this Letter we suggest a completely different approach, where we do not change the anomalous character, and retain the characteristics of the process. The main idea is to employ random death process and to 'kill' aging particles, for which the escape rate from the traps tends to zero as age tends to infinity.

The main aim of this Letter is to show that as long a death process is introduced, together with a particle production, the stationary solution of the modified fractional master equation is structurally stable whatever the spatial variations of anomalous exponent might be. In particular we use a regularized fractional master equation for the problem of morphogen gradient formation, which is a central topic of pattern formation in developmental biology [10]. Here we deal with a discrete fractional master equation and its continuous approximation, corresponding to a fractional Fokker-Planck equation.

Let us consider a random walk of particles on a semi-infinite lattice with unit length. The particle performs a random walk as follows: it waits for a random time T_k at each point k before making a jump to the right with probability $r(k)$ and left with the probability $l(k)$. We

denote the residence time probability density function by $\psi(k, \tau) = \frac{\partial}{\partial \tau} \Pr\{T_k < \tau\}$, and assume it has the Pareto form

$$\psi(k, \tau) = \frac{\nu(k)\tau_0^{\nu(k)}}{(\tau_0 + \tau)^{1+\nu(k)}},$$

where τ_0 is a constant with the unit of time, and $\nu(k)$ is the spatially dependent anomalous exponent: $0 < \nu(k) < 1$. We assume that during the time interval $(t, t + \Delta t)$ at point k the particle has a chance $\theta(k)\Delta t + o(\Delta t)$ of dying, where $\theta(k)$ is the death rate ($\theta(k) > 0$).

We denote by $p(k, t)$ the average number of particles at the point k at time t. The anomalous subdiffusive master equation with the death process can be written as

$$\frac{\partial p}{\partial t} = a(k-1)e^{-\theta(k-1)t}\mathcal{D}_t^{1-\nu(k-1)}[p(k-1,t)e^{\theta(k-1)t}]$$
$$+ b(k+1)e^{-\theta(k+1)t}\mathcal{D}_t^{1-\nu(k+1)}[p(k+1,t)e^{\theta(k+1)t}]$$
$$- (a(k) + b(k))e^{-\theta(k)t}\mathcal{D}_t^{1-\nu(k)}[p(k,t)e^{\theta(k)t}]$$
$$- \theta(k)p(k,t), \quad k \geq 2 \quad (2)$$

where

$$a(k) = \frac{r(k)}{\Gamma(1-\nu(k))\tau_0^{\nu(k)}}, \qquad b(k) = \frac{l(k)}{\Gamma(1-\nu(k))\tau_0^{\nu(k)}}.$$

are the anomalous rate functions. This fractional equation can be derived from a number of standpoints (see, for example, [14]). In this equation the anomalous exponent depends on the state, which is crucial for what follows. For the case of constant anomalous exponent ν, this reaction-transport equation and its continuous approximations were considered in [15–18].

To ensure the existence of stationary structure in the long time limit, we introduce the constant source term g at the boundary of the semi-infinite lattice ($k = 1$). This is crucial for the problem of morphogen gradient formation, where g models a localized source of morphogens [11]. We assume that the boundary is reflective, so we have the equation for $p(1,t)$

$$\frac{\partial p(1,t)}{\partial t} = b(2)e^{-\theta(2)t}\mathcal{D}_t^{1-\nu(2)}[p(2,t)e^{\theta(2)t}]$$
$$- a(1)e^{-\theta(1)t}\mathcal{D}_t^{1-\nu(1)}[p(1,t)e^{\theta(1)t}]$$
$$- \theta p(1,t) + g. \quad (3)$$

Note that any nonlinear function $g(p)$ can be included in (2).

Without the reaction ($\theta = 0$) the fractional master equation (2) with constant anomalous exponent ν is structurally unstable in the long time limit. The stationary solution $p_{st}(k) = \lim_{t\to\infty} p(k,t)$ can be found from (2) as

$$p_{st}(k) = p_{st}(1)\prod_{j=1}^{k-2}\frac{a(j)}{b(j+1)}, \qquad k \geq 2 \quad (4)$$

where

$$p_{st}(1) = \left(1 + \sum_{k=2}^{\infty}\prod_{j=1}^{k-1}\frac{a(j)}{b(j+1)}\right)^{-1}, \quad (5)$$

provided the sum is convergent. However, when the anomalous exponent is not constant, the asymptotic behavior is completely different. Consider the point M, at which the anomalous exponent is at a minimum $\nu(M) < \nu(k)$, $\forall k \neq M$. Then, one can show [7] that

$$p(M,t) \to 1, \qquad p(k,t) \to 0, \qquad t \to \infty. \quad (6)$$

As stated earlier, the main aim of this Letter is to regularize the fractional Master equation with the addition of the random death process. To this end, it is convenient to rewrite the fractional master equation as

$$\frac{\partial p(k,t)}{\partial t} = -I(k,t) + I(k-1,t) - \theta(k)p(k,t), \qquad k \geq 2 \quad (7)$$

where $I(k,t)$ is the total flux of cells from k to $k+1$

$$I(k,t) = a(k)e^{-\theta(k)t}\mathcal{D}_t^{1-\nu(k)}[p(k,t)e^{\theta(k)t}]$$
$$- b(k+1)e^{-\theta(k+1)t}\mathcal{D}_t^{1-\nu(k+1)}[p(k+1,t)e^{\theta(k+1)t}]. \quad (8)$$

The flux $I(k,t)$, in Laplace space takes the form

$$I(k,s) = a(k)(s+\theta(k))^{1-\nu(k)}\hat{p}(k,s)$$
$$- b(k+1)(s+\theta(k+1))^{1-\nu(k+1)}\hat{p}(k+1,s). \quad (9)$$

From here we can find the stationary flux $I_{st}(k) = \lim_{s\to 0} sI(k,s)$ as follows

$$I_{st}(k) = a^*(k)p_{st}(k) - b^*(k+1)p_{st}(k+1),$$

where

$$a^*(k) = a(k)[\theta(k)]^{1-\nu(k)}, \quad b^*(k) = b(k)[\theta(k)]^{1-\nu(k)}$$

and $p_{st}(k) = \lim_{s\to 0} sp(k,s)$. The main feature of this stationary flux is that it has Markovian form; but the rate functions $a^*(k)$ and $b^*(k)$ depend on the anomalous rate $a(k)$, $b(k)$, random death rate $\theta(k)$, and anomalous exponent $\nu(k)$. This unusual form of stationary flux is because of the non-Markovian character of subdiffusion.

Let us find the stationary distribution $p_{st}(k)$ for the simple case where θ is constant. In the long time limit, at the boundary, we then have the following condition:

$$I_{st}(1) = g - \theta p_{st}(1). \quad (10)$$

Similarly, we have the condition at the location $k = 2$ $I_{st}(2) = I_{st}(1) - \theta p_{st}(2)$. We are able to obtain a general expression for the stationary flux at location k

$$I_{st}(k) = g - \theta\sum_{j=1}^{k}p_{st}(j) \quad (11)$$

This has a very simple physical meaning: that as $t \to \infty$, $I_{st}(k)$ tends to the difference between the production rate and the sum of death rates at all states from the boundary up to k. It is clear that as $k \to \infty$, the stationary flux $I_{st}(k) \to 0$, since in the stationary state g should be equal to total death rate

$$g = \theta \sum_{j=1}^{\infty} p_{st}(j). \qquad (12)$$

We obtain

$$b(k+1)\theta^{-\nu(k+1)} p_{st}(k+1) = a(k)\theta^{-\nu(k)} p_{st}(k)$$
$$- \left(\frac{g}{\theta} - \sum_{j=1}^{k} p_{st}(j) \right)$$

This equation allows us to find $p_{st}(k)$ for all k. For the symmetrical random walk for which $a(k) = b(k) = a$ and $\nu = const$, we have

$$p_{st}(k+1) = p_{st}(k) - \frac{\theta^{\nu}}{a} \left(\frac{g}{\theta} - \sum_{j=1}^{k} p_{st}(j) \right). \qquad (13)$$

Now let us obtain the fractional Fokker-Planck equation with the death process, as the continuous limit of the master equation (2). We change the variables $k \to x$, $k \pm 1 \to x \pm l$ and take the limit $l \to 0$ to obtain

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x} \left[l \left(a(x) - b(x) \right) e^{-\theta(x)t} \mathcal{D}_t^{1-\nu(x)} [p(x,t)e^{\theta(x)t}] \right]$$
$$+ \frac{\partial^2}{\partial x^2} \left[\frac{l^2}{2} \left(a(x) + b(x) \right) e^{-\theta(x)t} \mathcal{D}_t^{1-\nu(x)} [p(x,t)e^{\theta(x)t}] \right]$$
$$- \theta(x)p(x,t). \qquad (14)$$

From this equation we obtain for $p_{st}(x) = \lim_{t \to \infty} p(x,t)$ the stationary advection-diffusion equation

$$-\frac{\partial}{\partial x} \left[v_{\nu}^{\theta}(x) \, p_{st}(x) \right] + \frac{\partial^2}{\partial x^2} \left[D_{\nu}^{\theta}(x) \, p_{st}(x) \right] = \theta(x)p_{st}(x),$$

where $v_{\nu}^{\theta}(x)$ is the drift, and $D_{\nu}^{\theta}(x)$ is the generalized diffusion coefficient defined as

$$v_{\nu}^{\theta}(x) = \frac{l \left(r(x) - l(x) \right) [\theta(x)]^{1-\nu(x)}}{\Gamma(1-\nu(x))(\tau_0)^{\nu(x)}},$$

$$D_{\nu}^{\theta}(x) = \frac{l^2 [\theta(x)]^{1-\nu(x)}}{2\Gamma(1-\nu(x))(\tau_0)^{\nu(x)}}.$$

This result means that in the long time limit, subdiffusion with the death process becomes standard diffusion with nonstandard drift $v_{\nu}^{\theta}(x)$ and diffusion coefficient $D_{\nu}^{\theta}(x)$. Both of them depend on the death rate $\theta(x)$ and the anomalous exponent $\nu(x)$. This is due to non-Markovian character of subdiffusion. It has been found in [16] that

the non-Markovian behavior of subdiffusion leads to an effective nonlinear diffusion. Note that the drift term $v_{\nu}^{\theta}(x)$ plays an essential role in chemotaxis, since $v_{\nu}^{\theta}(x) \sim \frac{\partial C}{\partial x}$, where C is the chemotactic substance. Therefore the dependence of chemotactic term of the degradation rate θ can be of great importance for the problem of cell aggregation [8, 19, 20].

Let us consider a random walk with a constant drift $v_{\nu}^{\theta} = -v$, diffusion D_{ν}^{θ}, and degradation rate θ. Then

$$v\frac{\partial p_{st}(x)}{\partial x} + D_{\nu}^{\theta}\frac{\partial^2 p_{st}(x)}{\partial x^2} - \theta p_{st}(x) = 0. \qquad (15)$$

The solution is the exponential profile

$$p_{st}(x) = A \exp \left[-\frac{v + \sqrt{v^2 + 4D_{\nu}^{\theta}\theta}}{2D_{\nu}^{\theta}} x \right], \qquad (16)$$

where A can be found from the condition $g = \theta \int_0^{\infty} p_{st}(x)dx$:

$$A = \frac{g \left(v + \sqrt{v^2 + 4D_{\nu}^{\theta}\theta} \right)}{2\theta D_{\nu}^{\theta}}. \qquad (17)$$

When $v_{\nu}^{\theta} = 0$, we have a morphogen profile obtained in [11]:

$$p_{st}(x) = \frac{g}{\sqrt{\theta D_{\nu}^{\theta}}} \exp \left[-\sqrt{\frac{\theta}{D_{\nu}^{\theta}}} x \right]. \qquad (18)$$

We now simulate the fractional master equation with random death process, (7), using Monte Carlo techniques. Throughout this we let $\tau_0 = 1$, so that this is the unit of time for the simulation; we take $g = 1$, so that we have a constant birth rate of one particle per unit time. The first particle begins a random walk at $k = 1$, such that at each point k waiting times are distributed as $\psi(k, \tau) = \frac{\nu(k)\tau_0^{\nu(k)}}{(\tau_0+\tau)^{1+\nu(k)}}$, and jump probabilities to the left and right from each point k are $r(k)$ and $l(k)$ respectively. A particle completes a random walk from when it is produced until the terminal time $t = T$, or until its random time of death exponentially distributed as $\psi_D(t) = \theta e^{-\theta t}$. This death rate is equivalent to a spatially invariant, constant death rate θ in (2). Also note that unlike the waiting time, the death time is not renewed when the particle makes a jump. The practical issue of having particles being produced and dying is dealt with in the following way. The first particle in the simulation begins at time $t = 0$, and completes its random walk as described above; the second particle begins at $t = 1$, because $\tau_0 = 1$, and completes its random walk; and so on until time $t = T$.

Firstly let us consider the symmetrical random walk, where $r(k) = l(k) = \frac{1}{2}$, $\nu(k) = 0.5$, and $\theta = 10^{-3}$. The figure FIG. 1 shows the corresponding stationary density made up from 10^4 realizations of the random walk at time $T = 10^6$.
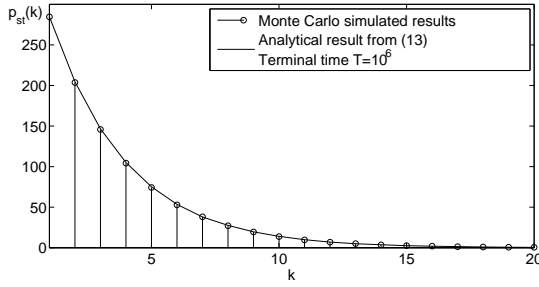
FIG. 1. Stationary profile for the symmetric fractional master equation where $r(k) = l(k) = \frac{1}{2}$, $\nu(k) = const. = 0.5$, $\tau_0 = 1$, and $\theta = 10^{-3}$.
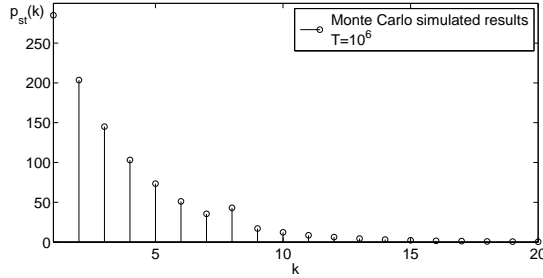

FIG. 2. Stationary profile for the symmetric fractional master equation, with a pertubation to the anomalous exponent at $k = 8$. $\nu(k \neq 8) = 0.5$, $\nu(8) = 0.4$

We can see that our simulation is in agreement with the analytical values calculated from the recurrence relation (13).

Next, we show that the model is robust to non-homogenous spatial perturbations in the anomalous exponent. Analogously to the simulation we presented in the previous work [7], we introduce a small perturbation to the anomalous exponent at one point in the space: all states have $\nu = 0.5$ except for $k = 8$, which has $\nu = 0.4$. From FIG. 2 we can see that although we observe a change to the stationary profile around point $k = 8$, the stationary profile is structurally stable and exponential in character. We stress the importance of the death process in regulating the behavior of the process to ensure stability. Whereas in our previous work, we showed that even a small perturbation in the anomalous exponent like this would lead to a breakdown in the stationary density. Additionally, we considered a non-symmetrical random walk which leads to a drift and found that the profile is stable.

In summary, we have suggested a new regularization of the subdiffusive fractional master equation by using the random death process. The fundamental feature of this approach is that unlike the previous regularization, which loses the anomalous characteristics, we are able to retain dependence on the anomalous exponent. We find the stationary flux of the particles has a Markovian form,

with unusual rate function depending on the anomalous rate functions, the death rate, and the anomalous exponent. We have shown that the long-time and continuous limit of this regularized fractional equation is the standard advection-diffusion equation that, importantly, is structurally stable with respect to spatial variations of anomalous exponent ν. We have found that the effective advection and diffusion coefficients, v_ν^θ and D_ν^θ, are increasing functions of the death rate θ: $v_\nu^\theta \sim D_\nu^\theta \sim \theta^{1-\nu}$. We have applied a regularized fractional master equation and modified fractional Fokker-Planck equation to the problem of the morphogen gradient formation. We have shown the robustness of the stationary morphogen distribution against spatial fluctuations of anomalous exponent.

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